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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,516	06/08/2000	CHRISTOPHER ROBERT BEBBINGTON	078883/0119	3014

22428 7590 02/19/2003

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EXAMINER
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ART UNIT	PAPER NUMBER
1632	29

DATE MAILED: 02/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/508,516	Bebbington et al.
Examiner	**Art Unit**
Michael C. Wilson	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *8-23-02 and 12-12-02*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 5, 6, 9-11, 14-17, 21, 22, 24, 30, and 46-59* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 5, 6, 9-11, 14-17, 21, 22, 24, 30, and 46-59* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's arguments filed 8-23-02, paper number 25, have been fully considered but they are not persuasive. The response filed 12-12-02, paper number 28, supplying support for the claim amendments has been entered. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 2-4, 7, 8, 12, 13, 18, 19, 23 and 42 have been canceled. Claims 46-59 have been entered. Claims 1, 5, 6, 9-11, 14-17, 21, 22, 24, 30 and 46-59 are pending and under consideration in the instant office action.

Claim Objections

The 3' and 5' LTR in line 1 of claim 1 should be item (a) as they are the first component of the vector. The other components should be (b)-(e).

Dependent claims 58 and 59 should begin "The...."

The phrase "a retroviral vector" in claim 24 should be --the retroviral vector--.

The quotation marks in claim 1 should be deleted.

The word "tile" in claim 47, step b) is incorrect.

Claim Rejections - 35 USC § 112

1. Claims 1, 5, 6, 9-11, 14-17, 21, 22, 24 and 30 remain rejected and 46-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The specification as originally filed does not provide support for a splice donor (SD) within a 5' LTR as claimed for reasons of record (claim 1). In the response filed 12-12-02, applicants state support for claim 1 is found on pg 25, lines 4-8; pg 29, lines 15-19; Example 2, pg 75, lines 12-30; Fig. 6; and the paragraph bridging pg 68-69. Applicants argument is not persuasive.

Pg 25, lines 4-8, and pg 29, lines 15-19, states the NOI is flanked by a splice donor (SD) and a splice acceptor (SA). The citations do not state the SD is within an LTR as claimed.

Example 2, pg 75, lines 12-30, Fig. 6 and the description of Fig. 6 on pg 68, line 28, teach inserting an SD at the border between the CMV promoter and the R/U3 of an LTR. The citation does not teach the SD is within the LTR as claimed because it is not flanked by nucleotides of the LTR. Instead, the SD is next to the LTR. The citation does not state the LTR is a 5' LTR as claimed. None of the vectors described on pg 75, lines 12-30 or in the paragraph bridging pg 68-69 have an SD within an LTR, specifically a 5' LTR, as claimed.

The specification as originally filed does not provide support for a vector having a) a 3' and 5' LTR, b) a SD and a SA, wherein the SD is within the 5' LTR, c) a first NOI flanked upstream by the SD and flanked downstream of the SA, and d) a second NOI downstream of the SA as claimed (claim 1). To reiterate, applicants state support for claim 1 is found on pg 25, lines 4-8; pg 29, lines 15-19; Example 2, pg 75, lines 12-30; Fig. 6; and the paragraph bridging

pg 68-69. None of these citations explicitly describe the vector claimed, especially none of the vectors in the Figures because they do not have two NOI and/or do not have a SD within a 5' LTR as claimed. None of these citations describe a vector that implicitly becomes the vector claimed upon reverse transcription and translocation of an LTR having a SD. See the discussion of the citations provided in the paragraphs above.

The "summary of the claimed invention" in the response filed 8-23-02, is noted. However, the summary does not correlate to the claimed vector because the summary does not discuss the first and second NOI required in the claims. In addition, the summary does not correlate to the disclosure because the vector described on pg 9, "vector in secondary target cells," is not explicitly or implicitly disclosed in the specification. The summary implies that the vector claimed is produced after reverse transcription which causes "U3-SD-R" to be translocated to the 5' LTR (pg 9 last para.); however, applicants have not pointed to any vector in the specification that would result in the vector claimed after reverse transcription. Overall, the vector claimed is not explicitly or implicitly disclosed in the specification. Therefore, claim 1 is new matter.

The arguments to the written description rejection in the response filed 8-23-02 are noted. Applicants refer to "the U3-SD-R sequences" on pg 11, line 8, but such a sequence is not described in the specification, lacks antecedent basis in applicants arguments and is not explicitly or implicitly described in Fig. 6-9 discussed in applicants arguments.

Applicants argue that "after transduction (reverse transcription), the 3' end of the pro-viral vector, i.e. the U3/SD/R region, is duplicated and translocated." (Pg 11, line 19, of arguments). The "U3/SD/R region" described in the argument is not described in the specification and lacks antecedent basis in applicants arguments. Therefore, it is unclear from where the "U3/SD/R region" came. The specification does not explicitly or implicitly teach any splice donor translocating from a 3' LTR to a 5' LTR, specifically to within a 5' LTR. The arguments do not correlate the merely translocating an LTR with the vector claimed which also has two NOI in specific locations.

The genus of a second NOI downstream of the splice acceptor site (claim 1) does not have support in the specification as originally filed and is considered new matter.

The limitation of an "NOI, or the expression product thereof," being "capable of providing a therapeutic agent or a diagnostic agent" (claim 5) is new matter. Applicants do not point to any support for the claim as amended. While the specification contemplates an NOI encoding a protein that is a therapeutic agent or a diagnostic agent, the claim as written is broader and encompasses NOI encoding proteins that cause the production of therapeutic or diagnostic agents. The breadth of NOI encompassed by the claim as written is not supported in the specification as originally filed.

The limitations of an SA "from a nucleotide sequence coding for an immunological molecule" (claim 15), "an immunoglobulin" (claim 16) or "an immunoglobulin heavy chain variable regions" (claim 17) are new matter. Applicants point to pg 25, lines 28-30, and 26, lines

1-6, for support. However, pg 25 describes a nucleotide sequence (NS) that is a coding sequence for an immunological molecule, pg 26, line 1, states the immunological molecule is an immunoglobulin, and pg 26, line 3, states the second NS is a coding sequence for an immunoglobulin heavy chain variable region. The claims do not require an "NS." The specification does not define "NS" as having an SA. The specification does not suggest isolating an SA from a coding sequence for an immunological molecule. Without such guidance, the specification does not support the claims.

The genus of "HIV" as newly claimed (claim 22 and 54) is new matter. Applicants have not provided support for this broader genus of viruses. Support is not found on pg 26, line 22, which describes HIV-1, as species of the genus claimed.

Claim 46 is new matter. The combination of elements claimed was not contemplated in the specification as originally filed. Applicants point to pg 25, lines 9-12, 8-30; Example 2 pg 73-77, and Fig. 14 and 17. Pg 25 does not describe a 5' LTR having an SD. Fig. 14 and 17 do not describe a sequence encoding an immunological molecule.

Claim 47 is new matter. Applicants state support is provided in Example 2, pg 73, lines 12-30; Fig. 6, legend para. bridging pg 68-69; Fig. 7-9. The starting material, i.e. the pro-viral vector having a SD within the 3' LTR is not described in the citations provided. The SD in Fig. 6-9 is not within the LTR - it is between the LTR and the CMV promoter. The SD in Fig. 6-9 is not within a 3' LTR. None of the vectors on pg 75 correlate to the starting vector required in the claim. Pg 75 does not describe any vectors that result in production of a vector having an SD

within its 5' LTR upon being transfected into "a host secondary cell". Therefore, the claim is new matter.

Claim 49 "wherein the first NOI is expressed in the host primary cell" is new matter. Applicants point to pg 33, lines 23-26, 28, 29; pg 44, lines 1-13, Fig. 17 and 27C. Pg 33 describes the structure of the first NOI and does not teach the first NOI is expressed, specifically in the host primary cell. Pg 44 states *env* is expressed in primary target cells and does not teach *env* is in the first NOI or describe "the host primary cell" as claimed. Fig. 17 and 27C describe vectors and do not describe a first NOI or expression in a host primary cell.

Support for the limitation in claim 50 ("wherein the first NOI is a selectable marker, a viral element or a combination thereof") is found in para bridging pg 32-33, pg 33, lines 23-29, as in claim 6 - not in pg 33, lines 23-29, pg 44, lines 1-13 and Fig. 17 and 27C as provided.

Claim 51 is new matter. Support cannot be found on pg 43, lines 18-20, pg 44, lines 5-13, Fig. 12, pg 77, lines 1-5, for a first NOI that has a packaging signal or retroviral envelope sequence or combination thereof. The specification does not contemplate such elements in the first NOI.

Claim 52 is new matter. Support for a retroviral packaging signal "upstream of the functional splice acceptor site" cannot be found on pg 77 or in Fig. 12. Neither pg 77 or Fig. 12 describe a packaging signal. Neither pg 77 or Fig. 12 describe preventing slicing of the first NOI in the primary host cell upon transfection.

Claim 55 is new matter. Applicants point to pg 30, lines 16-18, which does not teach the transcriptional control sequence is upstream of the SD as claimed.

Claim 56 is new matter. Pg 33, lines 23-25, 28-29 does not teach the first NOI is expressed. In fact, lines 23-25 states the first NOI has non-coding sequences. Lines 28-29 states the first NOI may encode viral elements such as *env* but does not teach the viral elements are expressed, specifically in primary cells as claimed.

Claim 57 is new matter. Pg 44, lines 9-12, does not teach the vector used or the vector obtained after reverse transcription and integration has an NOI downstream of the SA as claimed. Pg 77, lines 12-30, does not teach any vector having an SD within a 5' LTR, an SA, and an NOI downstream of the SA as claimed. Nor does it teach any vector that results in the vector claimed after reverse transcription and translocation.

In the future, please be specific and concise in providing support for claim amendments. For example, it is unclear why applicants believe Fig. 6 supports claim 1, why any vector described on pg 77, lines 12-30, is equivalent to the vector of claim 1 or why any vector described therein becomes the vector of claim 1. It is unclear what aspect of Fig. 14 and 17, describing the structure of numerous vectors, applicants believe supports claim 46. Therefore, the support provided is not specific. In addition, some citations provided as support appear to be extraneous. For example in claim 24, it is unclear why the citations other than those involving "retroviral particle" are provided, as claim 24 is equivalent to claim 1 except that it is a retroviral particle comprising the vector of claim 1. Therefore, the support provided is also not concise.

2. Claims 1, 5, 6, 9-11, 14-17, 21, 22, 24 and 30 remain rejected and 46-59 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for the selective expression of the hygromycin - neomycin gene pair or the hygromycin-p450 gene pair does not reasonably provide enablement for any nucleotide sequence of interest (NOI) as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for reasons of record.

Applicants repeat the argument that one of skill would be able to compensate for cryptic splice sites by identifying and altering the sites as taught by Sebillon (1995), Maruyama (1995) and Burns (1995). Applicants argument is not persuasive because it was unpredictable whether a gene contained a cryptic splice site. Therefore, it was unpredictable what gene to put into the vector claimed such that proper translocation and protein expression could be obtained. The specification does not overcome the unpredictability in the art by teaching how to make and/or use the vector claimed encoding any gene of interest having a cryptic splice site for reasons of record.

The specification does not enable making the retroviral vector claimed by mere reverse transcription. The translocation of the splice donor site upstream of the splice acceptor site is a result of reverse transcription which is not clearly set forth in the claims. Integration into the host cell's genome of the pro-virus results in addition of a functional intron which contains a nucleotide sequence of interest (NOI). Since the gene of interest is within the intron, no protein

from the gene will be expressed due to splicing out of the sequence; however, claims 49 requires expression of the NOI. Further, expression of a second gene of interest downstream of the splice acceptor site is activated because of the functioning intron. The first NOI has no function if there is no second NOI and does not function unless it is within an intron. The method of making the vector and translocation cannot be performed merely by reverse transcription as claimed. The essential elements describing the structure and function of the vector and pro-vector are not in the claims. The steps required to make the vector using the pro-vector are not in the claims.

Claim 5 recites the vector is capable of providing a therapeutic or diagnostic effect. The specification does not enable transfecting cells within a host or using the vector claimed for diagnosis or therapy for reasons of record. Applicants argue the specification provides adequate guidance for treating a subject by listing therapeutic and/or diagnostic molecules on pg 32, 33, 35. Applicants argument is not persuasive because the specification merely lists compounds used for therapy/diagnosis. The therapy/diagnosis is not discussed in the specification in context of gene therapy/diagnosis. The specification does overcome the unpredictability in the art of record for one of skill to obtain a therapeutic or diagnostic effect using a retroviral vector encoding the proteins claimed by providing the level of expression, route of delivery, target tissue and dosage required to obtain a therapeutic/diagnostic effect.

3. Claims 1, 5, 6, 9-11, 14-17, 21, 22, 24 and 30 remain and 46-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claim 1 as newly amended is indefinite because it is unclear if the second NOI can be the 3' LTR. The location of the 3' LTR in the vector in relationship to the first and second NOI and SA cannot be determined.

Claim 5 as newly amended is indefinite because the metes and bounds of an "NOI or expression product thereof," that is "capable of providing a therapeutic agent or diagnostic agent" is unclear. It is unclear whether the claim is limited to DNA encoding therapeutic or diagnostic proteins or if the claim encompasses any DNA or expression products that effect the "providing of a therapeutic or diagnostic agent." It is unclear whether the protein produced by the NOI is the agent or provides the agent.

The metes and bounds of the NOI in claim 6 cannot be determined. It is unclear if the claim is limited to NOI encoding marker proteins or viral proteins or if the claim encompasses DNA that can be used to select cells of interest, and/or viral non-coding regions.

Claim 14 is indefinite because it is unclear how the phrase "such that additional NOIs may be inserted" further limits the structure of function of the vector claimed. It is unclear if insertion of the multiple cloning sites results in the insertion of additional NOIs or if the phrase is describing a particular type of multiple cloning site.

Claim 15 remains indefinite because nucleic acid sequences cannot encode any "immunological molecule." Immunological molecules encompass non-proteins; however, nucleic acid sequences can only encode proteins. Therefore, the claim should be limited to immunological proteins.

"The retroviral particle" in claim 24 lacks antecedent basis in claim 1. Claim 24 is indefinite because it is a substantial duplicate of claim 1. The limitation of "comprises a functional splice donor site..." does not distinguish the retroviral vector of claim 24 from the retroviral vector of claim 1.

Claim 30 remains indefinite because a pro-viral vector is not defined in claim 1.

Claim 46 is indefinite because it is unclear how the "first nucleotide sequence (NS) comprising the functional splice donor site" further limits claim 1. It is unclear whether the first NS in claim 46 must also encompass the 5' LTR which has the splice donor site, if the first NS is the 5' LTR or if the first NS can have a fragment of the 5' LTR. It is also unclear if the first NS has a second copy of the SD or if the SD in claim 1 is within a "first NS"; however, the SD in claim 1 is already within a "first NS" as in claim 46 because it is within the 5' LTR which is considered a "first NS." As such, the metes and bounds of the structure of the first NS, SD and 5' LTR in the vector in claim 46 cannot be envisioned. Likewise, it is also unclear if the second NS has a second copy of the SA or if the SA in claim 1 is within a "second NS"; however, the SA in claim 1 is already within a "second NS" as claimed in 46 because in it is within the vector which

is considered a "second NS." As such, the metes and bounds of the structure of the second NS and SA in the vector in claim 46 cannot be envisioned.

The term "tile" in claim 47 is unclear.

New claim 47 is indefinite because it is unclear if the first NOI can be the 5' LTR. It is unclear if the "second NOI" can be the a fragment of the 3' LTR downstream of the SD. The location of the 5' LTR in the vector in relationship to the first and second NOI and SA cannot be determined.

The phrase "the packaged pro-viral vector" in claim 47 lacks antecedent basis. In addition, the step of packaging a as claimed results in a viral particle and not another pro-vector as claimed.

The step of infecting cells with a packaged vector does not "thereby cause reverse transcription" as claimed (claim 47). The enzyme reverse transcriptase causes reverse transcription. Infection of secondary cells may lead to reverse transcription and integration, but infection is not the cause of reverse transcription and integration as claimed.

It is unclear if the method of claim 47 results in one or two splice donor sites. It is unclear if applicants are claiming the SD in the last line within the 5' LTR is a copy of the SD in (i), or a different SD.

Claim 48 is indefinite. It is unclear if applicants are claiming the SD in claim 48 is a copy of the SD in claim 47 (i), the SD in the last line of claim 47, or a different SD.

Claim 51 is indefinite because packaging signals are not expressed as in parent claim 59.

Claim 52 is indefinite. It is unclear if the presence of the packaging signal prevents splicing or if expression of the packaging signal, as in parent claim 49, prevents splicing. It is also unclear if the limitation is further describing the "packaging" as requiring "transfecting" or if the limitation is merely setting forth the structure of the vector.

The metes and bounds of "transcriptional control sequence" in claim 55 is unclear. It is unclear if such a sequence encompasses the 3' and 5' LTR, SD and SA in the parent claims or is a sequence in addition to the sequences described in the parent claims. As such, the location of the "transcriptional control sequence" in the pro-vector cannot be determined.

Claim 56 is indefinite because it is unclear whether the "primary cell" is the "host primary cell" in the parent claim or some other cell.

Claim 57 is indefinite because it is unclear if the 3' LTR is considered an NOI downstream of the SA as claimed. Thus, the metes and bounds of the vectors encompassed by the claim cannot be determined.

The phrase "wherein the retroviral particle comprises a..." (Claim 58) is redundant because the retroviral vector of claim 57 already has an SD within its 5' LTR.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER